REMARKS/ARGUMENTS

Claims 21-34, 45, and 46 are now pending in the application as entered with the Amendment filed March 15, 2004. No further claim amendments are presented herein. The Examiner's comments in the Office Action are addressed below in the order set forth therein.

The Rejections of the Claims Under 35 U.S.C. §103(a) Should Be Withdrawn

Claims 21-34, 45, and 46 are rejected under 35 U.S.C. §103(a) as being obvious in view of Clark *et al.* (U.S. Patent No. 5,597,802; hereinafter the '802 patent). This rejection is respectfully traversed.

To establish a *prima facie* case of obviousness (1) there must be some suggestion in the reference or knowledge generally available to one of ordinary skill in the art to modify the reference or combine the references; (2) there must be a reasonable expectation of success; and (3) the prior art reference(s) must teach or suggest all the claim limitations. The teaching or suggestion . . . and the reasonable expectation of success must both be found in the prior art and not based on applicant's disclosure. MPEP § 2143, citing to *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). Applicants respectfully submit that this cited reference does not teach or suggest Applicants' claimed invention, particularly when the teachings of the reference *as a whole* are taken into consideration.

Applicants' invention is directed to IGF-I-containing compositions that comprise a buffer that consists substantially of succinate within a concentration range of about 10 mM to about 40 mM and a counterion (claims 21-34) or succinate within a concentration range of 7 mM to 45 mM and a counterion (claims 45 and 46). The Office Action acknowledges that these ranges are not taught by the '802 patent (Office Action mailed October 5, 2004, pages 3-4). Therefore, there must be some suggestion in this cited reference or knowledge generally available to one of ordinary skill in the art to modify this cited reference to arrive at Applicants' claimed invention, wherein IGF-I or variant thereof is formulated with succinate at the claimed concentration ranges.

As Applicants have previously noted, the '802 patent not only fails to teach the recited concentration ranges for succinate, it also merely mentions succinate buffer briefly in the following two passages:

> The carrier suitably contains minor amounts of additives such as substances that enhance isotonicity and chemical stability. Such materials are non-toxic to recipients at the dosages and concentrations employed, and include buffers such as phosphate, citrate, succinate, acetic acid, and other organic acids or their salts; antioxidants such as ascorbic acid; low molecular weight (less than about ten residues) polypeptides, e.g., polyarginine or tripeptides; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone; glycine; amino acids such as glutamic acid, aspartic acid, or arginine; monosaccharides, disaccharides, and other carbohydrates including cellulose or its derivatives, glucose, mannose, or dextrins; chelating agents such as EDTA; sugar alcohols such as mannitol or sorbitol; counterions such as sodium; nonionic surfactants such as polysorbates, poloxamers, or PEG; and/or neutral salts, e.g., NaCl, KCl, $MgCl_2$, $CaCl_2$, etc.

('802 patent, column 11, lines 41-58); and

> The "buffer" may be any suitable buffer that is GRAS and confers a pH of 5-6 on the GH+IGF-I formulation and a pH of about 5-5.5 on the IGF-I formulation. Examples include acetic acid salt buffer, which is any salt of acetic acid, including sodium acetate and potassium acetate, succinate buffer, phosphate buffer, citrate buffer, or any others known to the art to have the desired effect. *The most preferred buffer is sodium acetate, optionally in combination with sodium citrate.*

Applicants note that the Examiner has "the initial burden ... to provide some suggestion of the desirability of doing what the inventor has done" (M.P.E.P. §706.02(j), citing to *Ex parte Clapp*, 227 USPQ 972, 973 (Bd. Pat. Appl. & Inter. 1985). In the present case, Applicants respectfully submit that this burden has not been met because there is no teaching or rationale to modify the above passages to arrive at Applicants' claimed invention. Applicants respectfully submit that the Examiner solely derives the motivation or desirability of using succinate buffer from the fact that the '802 patent recites succinate buffer in a generic Markush group. As will be discussed *infra*, the inclusion of an element in a Markush group does not render an invention *prima facie* obvious absent any other specific rationale or desirability of using the recited element.

Specifically, the Examiner asserts that the rationale of using succinate buffer can be derived from the '802 patent because this patent recites this buffer in the equivalent of a Markush group (i.e., "use of succinate from a group of buffers containing *limited* [emphasis added] members"), and therefore the modifications are *prima facie* obvious (Office Action mailed

October 5, 2004, page 5). However, membership within a Markush group alone cannot be used to meet the burden of establishing a *prima facie* obviousness rejection. As the M.P.E.P. states, "[t]he mere fact that components are claimed as members of a Markush group cannot be relied upon to establish the equivalency of these components." M.P.E.P. §2144.06. Therefore, if the Examiner is asserting that the rationale for using succinate buffer is derived from its inclusion in a Markush group, the rejection is respectfully traversed, because no other evidence is presented as to the desirability of using succinate buffer to formulate IGF-I absent Applicants' disclosure.

In the alternative, if the recited elements are to be construed as belonging to a group of essentially unlimited members (in which case the '802 patent is only reciting a few examples), it still remains the Examiner's burden to explain why succinate would be a desirable buffer over others in the universe of all known buffers. The mere fact that the '802 patent discloses examples of some buffers known in the art does not provide the rationale or desirability of using succinate buffer with IGF-I specifically. Therefore, to the extent that the Examiner finds that the '802 patent discloses essentially an unlimited number of buffers (of which a few are explicitly named), the rejection is respectfully traversed because no rationale exists for the desirability of selecting succinate buffer to formulate IGF-I absent Applicants' disclosure.

Finally, to the extent that the Examiner is implicitly asserting that succinate is an "equivalent" buffer to those used in the actual IGF-I or IGF-I + GH formulations disclosed by the '802 patent, Applicants assert that the experimental data presented in this cited patent demonstrate that buffers used in such compositions are not equivalent. Specifically, Figures 13 through 24 of the '802 patent demonstrate that the biological effects of these formulations can vary significantly depending upon the buffer. For example, the percentage of blood glucose varied, at times, over 40% between subcutaneously injected acetate buffer formulations and citrate buffer formulations. Such variability of the bioactivity of IGF-I formulated with different buffers is indicative of the non-obviousness of Applicants' claimed invention.

Applicants again point to the statements in this cited patent as to the desirability of formulating IGF-I or IGF-I + GH with actetate buffers (see arguments presented on pages 3-4 of Applicants' response filed July 12, 2004). Thus, the teachings of this cited patent *as a whole* do

not suggest the desirability of formulating IGF-I with a succinate buffer, particularly succinate buffer within the claimed concentration ranges.

In view of these remarks, Applicants respectfully submit that the '802 patent not only fails to teach the succinate buffer ranges recited in the pending claims but also fails to provide the requisite motivation to modify the teachings therein to arrive at Applicants' claimed invention. Accordingly, this rejection of the claims should be withdrawn.

CONCLUSION

In view of the foregoing remarks, Applicants respectfully submit that the rejections of the claims under 35 U.S.C. §103(a) are overcome. Accordingly, the present application is now in condition for allowance. Early notice to this effect is solicited. If in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject Application, the Examiner is invited to call the undersigned.

It is not believed that extensions of time are required beyond those that may otherwise be provided for in documents accompanying this paper. However, in the event that additional extensions of time are necessary to allow consideration of this paper, such extensions are hereby petitioned under 37 CFR § 1.136(a), and any fee required therefore is hereby authorized to be charged to Deposit Account No. 16-0605.

Respectfully submitted,

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I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Mail Stop Amendment, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on January 4, 2005.

Lynda-Jo Pixley